

The Role of Insulin and Insulin-like Peptides in Ischemic Stroke and Cognitive Impairment

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademien, Göteborgs Universitet kommer att offentligens försvaras i hörsal Ivan Ivarsson, Medicinaregatan 3, fredagen den 25 november 2016, klockan 13.00

Av Daniel Åberg, leg läk

Fakultetsopponent:
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Avhandlingen baseras på följande delarbeten

- I. Åberg D, Jood K, Blomstrand C, Jern C, Nilsson M, Isgaard J, Åberg ND. Serum IGF-I levels correlate to improvement of functional outcome after ischemic stroke. *J Clin Endocrinol Metab.* 2011;96:E1055-E1064.
- II. Åberg ND, Olsson S, Åberg D, Jood K, Stanne TM, Nilsson M, Blomstrand C, Svensson J, Isgaard J, Jern C. Genetic variation at the IGF1 locus shows association with post-stroke outcome and to circulating IGF1. *Eur J Endocrinol.* 2013;169:759-765.
- III. Åberg D, Åberg ND, Jood K, Holmegaard L, Redfors P, Blomstrand C, Isgaard J, Jern C, Svensson J. Insulin resistance and outcome of ischemic stroke. 2016: manuscript.
- IV. Johansson P, Åberg D, Johansson J-O, Mattsson N, Hansson O, Åhrén B, Isgaard J, Åberg ND, Blennow K, Zetterberg H, Wallin A, Svensson J. Serum but not cerebrospinal fluid levels of insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 (IGFBP-3) are increased in Alzheimer's disease. *Psychoneuroendocrinology.* 2013; 38:1729-1737.
- V. Åberg D, Johansson P, Isgaard J, Wallin A, Johansson J-O, Andreasson U, Blennow K, Zetterberg H, Åberg ND, Svensson J. Increased cerebrospinal fluid level of insulin-like growth factor-II (IGF-II) in male patients with Alzheimer's Disease. *J Alzheimers Dis.* 2015;48:637-646.

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Abstract

Background and aims: Insulin, insulin-like growth factor-I (IGF-I), and the six high-affinity IGF-binding proteins (IGFBPs) play an important role in growth, metabolism and regeneration throughout the entire life span. In contrast, the role of IGF-II in adult life has been unclear. Animal studies have demonstrated that altered brain activity of the insulin/IGF-system is associated with reduced cognitive function and worse outcome after experimentally induced stroke and this is reversed by IGF-I-treatment. The overall aim of this thesis was to determine whether the insulin/IGF-I system is of importance for outcome of ischemic stroke (IS) also in humans and whether insulin and insulin-like peptides are dysregulated in patients with Alzheimer's disease (AD).

Patients and methods: Two well-characterized clinical cohorts were studied. In SAHLSIS (Sahlgrenska Academy Study on Ischemic Stroke; originally 600 IS patients and 600 population-based controls), characterization of patients after IS included serum samples and stroke scales. Furthermore, serum and cerebrospinal fluid (CSF) levels of insulin, IGF-I, and IGF-II were determined in a cross-sectional study of patients (n=60) with AD and other forms of cognitive impairment, and healthy controls (n=20).

Results: In *Paper I*, high serum IGF-I concentrations were associated with better improvement of functional independence in SAHLSIS. In *Paper II*, analyses of single-nucleotide polymorphisms (SNPs) in the *IGF1* gene showed that the major allele of rs7136446 was associated with favorable post-stroke outcome after 2 years. In *Paper III*, insulin resistance was associated with functional outcome, especially in patients with cryptogenic stroke. In *Paper IV*, serum but not CSF levels of IGF-I were increased in patients with AD whereas insulin levels were unchanged both in serum and CSF. In *Paper V*, CSF IGF-II level was increased in male but not in female patients with AD.

Conclusions: The IGF-I/insulin system is associated with functional outcome after ischemic stroke. Furthermore, levels of IGF-I and IGF-II are dysregulated in Alzheimer's disease.

Keywords: Ischemic Stroke (IS), Alzheimer's disease (AD), Cognitive Impairment, Dementia, Insulin-like Growth Factor I (IGF-I)

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